Robust H_∞ Feedback Control for Uncertain Stochastic Delayed Genetic Regulatory Networks with Additive and Multiplicative Noise

Wei Pan, Zidong Wang* and Huijun Gao

Abstract

Noises are ubiquitous in genetic regulatory networks (GRNs). Gene regulation is inherently a stochastic process because of intrinsic and extrinsic noises that cause kinetic parameter variations and basal rate disturbance. Time-delays are usually inevitable due to different biochemical reactions in such GRNs. In this paper, a delayed stochastic model with additive and multiplicative noises is utilized to describe stochastic GRNs. A feedback gene controller design scheme is proposed to guarantee that the GRN is mean-square asymptotically stable with noise attenuation, where the structure of the controllers can be specified according to engineering requirements. By applying control theory and mathematical tools, the analytical solution to the control design problem is given, which helps to provide some insight into synthetic biology and systems biology. The control scheme is employed in a three gene network to illustrate the applicability and usefulness of the design.

Keywords

Genetic regulatory networks (GRNs), Robust H_∞ feedback control, Noise attenuation, Time delay.

I. Introduction

It is well known that genetic regulatory networks are subject to noise disturbances that might occur at various stages such as transcription, translation, transport, chromatin remodeling and pathway specific regulation. Generally speaking, the noise sources could be partitioned into two categories: intrinsic noise and extrinsic noise [1]. Intrinsic noise is determined by the structure, reaction rates, and species concentrations of the underlying biochemical networks [2]. Intrinsic noises can be further classified as intrinsic noise in the specific gene as well as transmitted intrinsic noise from the upstream genes. The intrinsic noise arises mostly from low copy numbers of mRNAs [3–5]. The transmitted intrinsic noise, which includes the transmitted fluctuations of each of the upstream genes in the network, depends on three factors: 1) the intrinsic noise for that upstream gene; 2) the effect of temporal averaging [5, 6] dependent on the lifetimes of the proteins; and 3) the susceptibility of the downstream gene to the upstream one. on the other hand, differences between

This work was supported in part by the Biotechnology and Biological Sciences Research Council (BBSRC) of the U.K. under Grant BB/C506264/1, an International Joint Project sponsored by the Royal Society of the U.K., the National Natural Science Foundation of China under Grants 60504008, 60774073 and 60804028, the Program for New Century Excellent Talents in Universities of China, and the Alexander von Humboldt Foundation of Germany.

W. Pan is with the Space Control and Inertial Technology Research Center, Harbin Institute of Technology, Harbin 150001, China, and is also with the Department of Electronic Science and Technology, University of Science and Technology of China, Hefei 230027, China.

Z. Wang is with the Department of Information Systems and Computing, Brunel University, Uxbridge, Middlesex, UB8 3PH, United Kingdom.

H. Gao is with the Space Control and Inertial Technology Research Center, Harbin Institute of Technology, Harbin 150001, China.

*Corresponding author. Email: Zidong.Wang@brunel.ac.uk.

cells, either in local environment or in the concentration or activity of any factor that affects gene expression, will result in extrinsic noise. Extrinsic noises can be further divided into two categories [6, 7]: global noise (or fluctuations in the rates of the basic reactions that affect expression of all genes) and gene or pathway-specific extrinsic noise.

As pointed out in [34], the stochastic differential equation or the Langevin equation has recently been employed to describe the molecular fluctuation in GRNs [8, 9, 11, 12, 28, 29, 35, 36]. Many algorithms have been developed for simulating the Langevin equation to calculate the probability density function [2–4, 10]. The Fokker-Plank equation has been used to describe the evolution of the probability function [13, 14]. Most researchers have analyzed these stochastic models, via the Monte Carlo method such as the Gillespie algorithm [15], to reflect the evolution of biochemical networks through the discrete stochastic model. On the other hand, if biochemical process delays are not considered in modeling biochemical GRNs, the engineered biochemical network based on such model may lead to fluctuation, oscillation or even blowing up [16]. Therefore, time delays should be taken into account the dynamic model to mimic the realistic cellular behaviors of GRNs in cell. In this sense, a systematic design method for noise-attenuated and delay-insensitive robust GRNs is an important topic in synthetic biology and systems biology for an engineered GRN to work properly in host cells [17].

The GRN diagrams that resemble complex electrical circuits are generated by the connectivity of genes and proteins. Similar to electrical circuits, mathematical and computational tools have been utilized in developing circuits and systems using biotechnological design principles of synthetic GRNs, which include new kinds of integrated circuits like neurochips learnt from biological neural networks [9,18,19]. A basic theme for electrical circuits design is the feedback. The notion of feedback is also a central recurring theme in gene circuits. In fact, feedback is so prevalent in biological systems that it can be found at all levels of organization, from the molecular and cellular levels, to the organism and ecological levels [20]. It is impossible to overstate the importance of feedback as a strategy for the maintenance and evolution of life. Since feedback is the central topic in control theory, it is reasonable to expect that ideas from control theory will lead to new understanding of the underlying biological processes [21]. Applying control theory to study biology is fast becoming an interesting and exciting idea, although there exist large differences in culture, approach and the tools used in these two fields.

From the perspective of control engineering, the H_∞ control problem has long been regarded as an important issue in control community since H_∞ performance is an important index when evaluating the noise disturbance rejection attenuation [22,23]. From the perspective of latest synthetic biology and systems biology, if a concrete gene controller design scheme could be given, the research would be greatly facilitated in these areas. In this case, the H_∞ control strategy serves as a feasible and interesting candidate for designing gene regulatory networks. Unlike the external control in control engineering where the inputs are used by the conventional robust control designs [24], the *gene controller* under consideration is embedded in the GRNs, and our aim is to design an H_∞ feedback gene controller so that the GRN is mean-square asymptotically stable with a given noise attenuation level γ. Since the structure of the feedback controller gain has close relationship with the binding site of gene circuits, it is desirable for the designer to specify the structure of the controller, hence making a compromise among the performance, the technological limit as well as the cost.

In this paper, we are concerned with two research issues. One issue is the modeling of time delayed GRNs. Our model is based on the Langevin approach [25,26], in which the deterministic differential equations describing the dynamics of the system are modified by adding stochastic terms [14] that reflect the noise from

different sources: intrinsic noise due to low numbers of molecules and extrinsic noise in cellular components that change the reaction rates for all genes [6]. Different sources of noise are introduced to model kinetic parameter variations and basal rate disturbance. A delayed stochastic model with additive and multiplicative noises is utilized to describe the GRNs. The other issue is the design of robust feedback gene controller for improving the robustness of delayed GRNs based on H_∞ control theory. Two particular features of our design are that 1) the structure of the controllers can be specified *a priori*; and 2) the analytical expression of the feedback gain is given. These two features would help facilitate the research in synthetic biology and systems biology. Finally, the control scheme has been employed in a three gene network to illustrate the applicability and usefulness of the design.

Notation: The notation used throughout the paper is fairly standard. The superscript T stands for matrix transposition; $\mathbb{R}^n$ denotes the n-dimensional Euclidean space; $0_{m,n}$ represents a zero matrix with $m \times n$ dimensions; $L_2[0,\infty)$ is the space of square-integrable vector functions over $[0,\infty)$; $\|\cdot\|$ denotes the Euclidean norm for vector or the spectral norm of matrices; $\|\cdot\|_2$ stands for the usual $L_2[0,\infty)$ norm; $(\Omega,\mathcal{F},\mathcal{P})$ is a probability space, where Ω is the sample space, $\mathcal{F}$ is the σ-algebra of subsets of the sample space and $\mathcal{P}$ is the probability measure on $\mathcal{F}$; $\mathbf{E}\{\cdot\}$ stands for the expectation operator and $\mathbf{Cov}\{\cdot\}$ stands for the covariance operator with respect to some probability measure $\mathcal{P}$ respectively. The notation $X > 0$ (≥ 0) is used to denote a symmetric positive-definite (positive-semidefinite) matrix. In symmetric block matrices or complex matrix expressions, we use an asterisk * to represent a term that is induced by symmetry and diag$\{\ldots\}$ stands for a block-diagonal matrix. Matrices, if their dimensions are not explicitly stated, are assumed to be compatible for algebraic operations.

II. The Models and Problem Formulation

A. The Deterministic Model

The activities of a gene are regulated by other genes through the interactions between them, i.e., the transcription and translation factors. Here, regulation can be regarded as the feedback. Taking the time delay into account, the following delayed GRN model has been proposed in [27, 30]:

$$\begin{aligned} \frac{dm_i(t)}{dt} &= -e_i m_i(t) + \sum_j G_{ij} g_j(p_j(t-\tau)) + l_i, \\ \frac{dp_i(t)}{dt} &= -c_i p_i(t) + d_i m_i(t-\tau), \quad i = 1,2,...,n, \end{aligned} \tag{1}$$

where $m_i(t)$, $p_i(t) \in \mathbb{R}$ are concentrations of mRNA and protein of the ith node at time t, respectively, a_i and c_i are the degradation rates of the mRNA and protein, d_i is the translation rate, and $g_j(x) = (x/\beta_j)^H / \left[1 + (x/\beta_j)^H\right]$ is a monotonically increasing function with H as the Hill coefficient and β as a positive constant. The matrix $G = (G_{ij}) \in \mathbb{R}^{n\times n}$ is the coupling matrix of the GRN. l_i is defined as a basal rate.

System (1) can be written into the compact matrix form

$$\begin{aligned} \frac{dm(t)}{dt} &= Em(t) + Gg(p(t-\tau)) + l, \\ \frac{dp(t)}{dt} &= Cp(t) + Dm(t-\tau), \end{aligned} \tag{2}$$

where $m(t) = [m_1(t),\ldots,m_n(t)]^T$, $p(t) = [p_1(t),\ldots,p_n(t)]^T$, $E = \text{diag}\{-\text{e}_1,\ldots,-\text{e}_\text{n}\}$, $C = \text{diag}\{-\text{c}_1,\ldots,-\text{c}_\text{n}\}$, $D = \text{diag}\{-\text{d}_1,\ldots,-\text{d}_\text{n}\}$, $l = [l_1,\ldots,l_n]^T$ and $g(p(t-\tau)) = [g_1(p_1(t-\tau)),\ldots,g_n(p_n(t-\tau))]^T$.

Letting $[(p^*)^T,(m^*)^T]^T$ be an equilibrium of (2), the following relationships are obtained

$$\begin{aligned} 0 &= Em^* + Gg(p^*) + l, \\ 0 &= Cp^* + Dm^*. \end{aligned} \tag{3}$$

We now shift the equilibrium $[(p^*)^T,(m^*)^T]^T$of system (2) to the origin. Using the transformation $\hat{m}(t) = m(t) - m^*$, $\hat{p}(t) = p(t) - p^*$, system (2) can be converted into the following form:

$$\begin{aligned} \frac{d\hat{m}(t)}{dt} &= E\hat{m}(t) + Gh(\hat{p}(t-\tau)), \\ \frac{d\hat{p}(t)}{dt} &= C\hat{p}(t) + D\hat{m}(t-\tau), \end{aligned} \tag{4}$$

where $\hat{m}(t) = [\hat{m}_1(t),\ldots,\hat{m}_n(t)]^T$, $\hat{p}(t) = [\hat{p}_1(t),\ldots,\hat{p}_n(t)]^T$, and $h(\hat{p}(t-\tau)) = [h_1(\hat{p}_1(t-\tau)),\ldots,h_n(\hat{p}_n(t-\tau))]^T$ with

$$h_j(\hat{p}_j(t)) = g_j(\hat{p}_j(t) + p_j^*) - g_j(p_j^*). \tag{5}$$

Therefore, we arrive at the following delayed GRN:

$$\frac{dy(t)}{dt} = \hat{A}y(t) + \hat{B}\hat{f}(y(t-\tau)), \tag{6}$$

where

$$\begin{aligned} \hat{A} &= \begin{bmatrix} E & 0 \\ 0 & C \end{bmatrix}, \hat{B} = \begin{bmatrix} 0 & G \\ D & 0 \end{bmatrix}, \\ y(t) &= \begin{bmatrix} \hat{m}(t) \\ \hat{p}(t) \end{bmatrix}, \hat{f}(y(t-\tau)) = \begin{bmatrix} \hat{m}(t-\tau) \\ h(\hat{p}(t-\tau)) \end{bmatrix}. \end{aligned} \tag{7}$$

Note that it is usually not sufficient to describe a GRN with only mRNAs and proteins. Based on the model above, a more general GRN model is proposed as follows:

$$\dot{x}(t) = Ax(t) + Bf(x(t-\tau)), \tag{8}$$

where $x_1,\ldots,x_n$ are metabolites, such as genes, proteins, activators, repressors, enzymes, factors or products of a biochemical network, and $x(\cdot) = [x_1(\cdot),\ldots,x_n(\cdot)]^T \in \mathbb{R}^n$ is the metabolites state vector. Their rates of degradation are denoted by $a_i \in \mathbb{R}^+$. $\dot{x}_i$, the rate of change in x_i, represents concentration change of a variable due to production or degradation. $f(\cdot) = [f_1(\cdot),\ldots,f_n(\cdot)]^T$ represents the regulation function on the ith metabolite, which is generally a nonlinear or linear function on the variables $[x_1(\cdot),\ldots,x_n(\cdot)]$, but has a form of monotonicity with each variable. Generally speaking, A defines the degradation parameters matrix with non-diagonal plane elements zero, B defines the coupling topology, direction, and the transcriptional rate of the GRN [31].

Remark 1: Consider a nonlinear function representing the vector of reaction rates:

$$\dot{x}(t) = R(x(t)), \tag{9}$$

where $x(t)$ and $R(x(t))$ represent the concentrations and the rate law, respectively. By global linearization [32, 33], we get a linear GRN model $\dot{x}(t) = Ax(t)$. Generally speaking, elements on the diagonal plane of stoichiometric matrix A represent the degradation parameters, transcription or translation degree parameters can be attributed to the non-diagonal plane elements [31].

B. Additive Noise

The noise, especially external noise, affects the basal production rate directly. Based on the Langevin approach [25, 26], a noise term is appended to the deterministic model [14] which gives rise to the following Langevin equation

$$\dot{x}(t) = Ax(t) + Bf(x(t-\tau)) + \sum_{j=1}^{q} E_j \xi_j(t). \tag{10}$$

As the intensity of the white noise can be absorbed to E_j, $\xi_j(t)$ $(j = 1, \ldots, q)$ is assumed to be the additive white noise that is of the following statistical property

$$\begin{aligned} \mathbf{E}\{\xi_j(t)\} &= 0, \\ \mathbf{Cov}\{\xi_j(t)\xi_j(t')\} &= \delta(t-t'), \\ \mathbf{Cov}\{\xi_i(t)\xi_j(t)\} &= 0, \ (i \neq j), \end{aligned}$$

which also implies that noises from different sources are independent.

Using the equivalent Itô-type representation, the following stochastic GRN model is obtained:

$$dx(t) = [Ax(t) + Bf(x(t-\tau))]\,dt + \sum_{j=1}^{q} E_j d\omega_j(t), \tag{11}$$

where the vector process $\omega(t) = (\omega_1(t), \ldots, \omega_q(t))$ is a standard Wiener process. That is, $\omega_i(t)$, $i = 1, \ldots, q$, is a one-dimensional Brownian motion defined on a complete probability space $(\Omega, \mathcal{F}, \mathcal{P})$ and satisfies

$$\mathbf{E}\{d\omega_i(t)\} = 0, \ \mathbf{E}\{d\omega_i^2(t)\} = dt, \ \mathbf{E}\{d\omega_i(t)d\omega_j(t)\} = 0, (i \neq j).$$

C. Multiplicative Noise

It is noted that that acquiring parameters of the model are dependent on the selection of fixed point and relevant constant term, which in turn rely on the experiment data. On the other hand, the random behavior manifests the existence of noises during the process of gene expression, from the level of promoter binding to mRNA translation to protein degradation. The quality of GRN models may suffer from noises, especially intrinsic noises, which will lead to the kinetic parameter variations. To reflect such a reality, we introduce uncertain matrices $\triangle A(t)$ and $\triangle B(t)$ into (10) by allowing the parameters of A and B to vary stochastically and then obtain the following Langevin equation

$$\dot{x}(t) = (A + \triangle A)\,x(t) + (B + \triangle B)\,f(x(t-\tau)) + \sum_{j=1}^{q} E_j \xi_j(t), \tag{12}$$

where the uncertainties $\triangle A$ and $\triangle B$ are of the following structure

$$\triangle A = \sum_{j=1}^{q} C_j \xi_j(t), \ \ \triangle B = \sum_{j=1}^{q} D_j \xi_j(t).$$

Then we have the following model

$$\dot{x}(t) = Ax(t) + Bf(x(t-\tau)) + \sum_{j=1}^{q} \left[C_j x(t) + D_j f(x(t-\tau)) + E_j\right] \xi_j(t), \tag{13}$$

The scope of uncertainty can be measured by C_j and D_j. Of course, if some elements of A or B are free of noise disturbances, the corresponding elements of $\triangle C$ or $\triangle D$ should be equal to zero.

To sum up, we have come up with the following stochastic GRN model

$$\begin{aligned} dx\left(t\right) &= \left[Ax(t) + Bf\left(x\left(t-\tau\right)\right)\right]dt + \sum_{j=1}^{q}\left[C_j x(t) + D_j f\left(x\left(t-\tau\right)\right) + E_j\right]d\omega_j(t), \\ z\left(t\right) &= Fx\left(t\right), \\ x\left(t\right) &= \phi\left(t\right), \quad \forall t \in [-\tau, 0], \end{aligned} \tag{14}$$

where $x(t) \in \mathbb{R}^n$ is the state; $z\left(t\right)$ denotes the concentration of some genes or proteins that we are interested in; $\phi\left(t\right)$ is a real-valued continuous initial function on $[-\tau, 0]$. F is a known real constant matrix with appropriate dimensions. If we want to discuss the dynamics of the GRN as a whole, then we can let $F = I$.

Definition 1: The GRN model (14) with $E_j = 0$, $j = 1, \ldots, q$, is said to be mean-square stable if, for any $\varepsilon > 0$, there is a $\delta\left(\varepsilon\right) > 0$ such that

$$\mathbf{E}\left\|x(t)\right\|^2 < \varepsilon, \ t > 0,$$

when

$$\sup_{-\tau \le s \le 0} \mathbf{E}\left\|\phi\left(s\right)\right\|^2 < \delta\left(\varepsilon\right).$$

If, in addition,

$$\lim_{t\to\infty} \mathbf{E}\left\|x(t)\right\|^2 = 0$$

holds for any initial conditions, then the GRN model (14) with $E_j = 0$, $j = 1, \ldots, q$, is said to be mean-square asymptotically stable.

Definition 2: Given a scalar $\gamma > 0$, the GRN (14) is said to be robustly stochastically stable with noise attenuation γ if it is robustly stochastically stable and, under zero initial conditions,

$$\left\|z\left(t\right)\right\|_{E_2} < \gamma \sum_{j=1}^{q} \left\|n_j\left(t\right)\right\|_2$$

for all nonzero $n_j(t) \in L_2[0, \infty)$, where

$$\left\|z\left(t\right)\right\|_{E_2} = \left(\mathbf{E}\left\{\int_0^\infty \left\|z\left(t\right)\right\|^2 dt\right\}\right)^{1/2}, \quad \left\|n_j\left(t\right)\right\|_2 = \left\|E_j\xi_j(t)\right\|_2 = \left(E_j^T E_j\right)^{1/2}.$$

To establish our main results, it is necessary to make the following assumption and lemmas.

Assumption 1: Each function g_j in (1), $g_j\left(\cdot\right)$, $j = 1, 2, \ldots, n$, satisfies the following condition:

$$l_j^- \le \frac{g_j\left(x\right) - g_j\left(y\right)}{x - y} \le l_j^+ \ , \ \forall x, y \in \mathbb{R}, \ x \ne y, \ i = 1, 2, \ldots, n, \tag{15}$$

where l_j^- and l_j^+ are nonnegative constants.

By (5), (7) and Assumption 1, it is not difficult to verify that

$$l_j^- \le \frac{f_j\left(x\right)}{x} \le l_j^+, \ \forall x_i \ne 0, \ i = 1, 2, \ldots, n \tag{16}$$

with $f_j\left(0\right) = 0$.

Lemma 1: [37] For any vectors x, $y \in \mathbb{R}^n$ and matrix $P > 0$, we have

$$2x^T y \le x^T P^{-1} x + y^T P y.$$

Lemma 2: (Schur complement [38]) The following inequality

$$\begin{pmatrix} Q(x) & S(x) \\ S^T(x) & R(x) \end{pmatrix} > 0$$

where $Q(x) = Q^T(x)$, $R(x) = R^T(x)$ and $S(x)$ depend affinely on x, is equivalent to $Q(x) > 0$ and $Q(x) - S^T(x)R^{-1}(x)S(x) > 0$.

In this paper, we aim to deal with the problems of robust H_∞ feedback control for GRN model with additive and multiplicative noise described in (14).

D. The closed-loop system

We are interested in designing a feedback gene controller $Kx(t)$ for the GRN. The closed-loop system is given as follows

$$\begin{aligned} dx(t) &= [(A+K)x(t) + Bf(x(t-\tau))]\,dt + \sum_{j=1}^{q} [C_j x(t) + D_j f(x(t-\tau)) + E_j]\,d\omega_j(t), \\ z(t) &= Fx(t), \\ x(t) &= \phi(t), \quad \forall t \in [-\tau, 0], \end{aligned} \tag{17}$$

where K is the feedback gain matrix of the gene controller to be designed, in which k_{ij} denotes the feedback gain parameter to be specified for the gene controller between genes j and i. The gene controller from genes j to i can be implemented by inserting the motif binding site of gene product j into the promoter region of gene i so that the protein of gene j could bind this inserted motif-binding site to act as a transcription factor (TF) to regulate the gene expression of gene i.

E. The performance index

In this paper, the following performance index for a prescribed $\gamma > 0$ is considered:

$$J(t) = \mathbf{E}\left\{ \int_0^t [z^T(s)z(s) - \gamma^2 \sum_{j=1}^{q} E_j^T E_j] ds \right\}. \tag{18}$$

The problem to be tackled is formulated as follows. For the stochastic delayed GRN (14) and a given scalar $\gamma > 0$, we like to design a feedback gene controller $Kx(t)$ such that the resulting closed-loop system (17) is robustly stochastically stable with noise attenuation level γ. In this case, GRN (14) is said to be robustly stochastically stabilizable with noise attenuation level γ.

III. H_∞ Performance Analysis

This section is concerned with the H_∞ performance analysis problem. More specifically, supposing that the feedback controller gain matrix K in (17) is known, we will study the conditions under which the closed-loop system (17) is mean-square asymptotically stable with the noise attenuation level γ. The following theorem shows that the H_∞ performance of the closed-loop system can be guaranteed if there exist some matrices satisfying certain linear matrix inequalities (LMIs).

Theorem 1: Consider the stochastic delayed GRN (14) and suppose the feedback gene controller gain matrix K in (17) is given. For a scalar $\tau > 0$, the closed-loop system (17) is mean-square asymptotically stable with

the noise attenuation level γ if there exist matrices $P>0$, $Q>0$, $S>0$, $R>0$, $T^{-}=\mathrm{diag}\{\mathrm{t}_1^{-},\ldots,\mathrm{t}_\mathrm{n}^{-}\}\geq 0$, $T^{+}=\mathrm{diag}\{\mathrm{t}_1^{+},\ldots,\mathrm{t}_\mathrm{n}^{+}\}\geq 0$ and X satisfying

$$\left[\begin{array}{ccc}\Sigma_1+\Sigma_2 & X & \sqrt{\tau}X\\ * & -R & 0\\ * & * & -S\end{array}\right]<0, \tag{19}$$

where

$$\begin{aligned}
\Sigma_1 &= \Theta_1+\Theta_2+\Theta_2^T+\Theta_3,\ \Sigma_2=\Xi_1+\Xi_2+\Xi_3,\\
\Theta_1 &= W_x^TQW_x-W_h^TQW_h-2W_f^TT^{+}W_f+2W_f^TT^{-}W_f,\\
\Theta_2 &= W_x^TPW_y+XW_X+W_h^TT^{+}L^{+}W_f-W_h^TT^{-}L^{-}W_f,\ \Theta_3=-\gamma^2\sum_{j=1}^{q}W_{v_j}^TW_{v_j},\\
L^{-} &= \mathrm{diag}\{\mathrm{l}_1^{-},\ldots,\mathrm{l}_\mathrm{n}^{-}\},\mathrm{L}^{+}=\mathrm{diag}\{\mathrm{l}_1^{+},\ldots,\mathrm{l}_\mathrm{n}^{+}\},\\
\Xi_1 &= \tau W_y^TSW_y,\ \Xi_2=\sum_{j=1}^{q}W_{g_j}^T\left(P+\tau R\right)W_{g_j},\ \Xi_3=W_z^TW_z,\\
W_x &= \left[\begin{array}{ccc}I_n & 0_{n,2n+q}\end{array}\right],\ W_f=\left[\begin{array}{ccc}0_{n,2n} & I_n & 0_{n,q}\end{array}\right],\\
W_h &= \left[\begin{array}{ccc}0_n & I_n & 0_{n,n+q}\end{array}\right],\ W_y=\left[\begin{array}{ccc}A+K & 0_n & B & 0_n,q\end{array}\right],\\
W_X &= \left[\begin{array}{ccc}I_n & -I_n & 0_{n,n+q}\end{array}\right],\ W_{v_j}=\left[\begin{array}{ccc}0_{n,3n} & 0_{n,j-1} & E_j & 0_{n,q-j}\end{array}\right]\\
W_{g_j} &= \left[\begin{array}{ccc}C_j & 0_n & D_j & 0_{n,j-1} & E_j & 0_{n,q-j}\end{array}\right],\ W_z=\left[\begin{array}{ccc}F & 0_{n,2n+q}\end{array}\right],\ .
\end{aligned} \tag{20}$$

Proof: For convenience, set

$$\begin{aligned}
y\left(t\right) &= \left(A+K\right)x\left(t\right)+Bf\left(x\left(t-\tau\right)\right),\\
g_j(t) &= C_jx(t)+D_jf\left(x\left(t-\tau\right)\right)+E_j.
\end{aligned} \tag{21}$$

The first equation in (17) can be rewritten as

$$dx\left(t\right)=y\left(t\right)dt+\sum_{j=1}^{q}g_j\left(t\right)d\omega_j\left(t\right). \tag{22}$$

Define the following Lyapunov-Krasovskii functional candidate for system (17)

$$\begin{aligned}
V(t) &= V_1(t)+V_2(t)+V_3(t)+V_4(t),\\
V_1(t) &= x^T(t)Px(t),\\
V_2(t) &= \int_{t-\tau}^{t}x^T(\alpha)Qx(\alpha)d\alpha,\\
V_3(t) &= \int_{-\tau}^{0}\int_{t+\beta}^{t}y^T(\alpha)Sy(\alpha)d\alpha d\beta,\\
V_4(t) &= \sum_{j=1}^{q}\int_{-\tau}^{0}\int_{t+\beta}^{t}g_j^T(\alpha)Rg_j(\alpha)d\alpha d\beta,
\end{aligned} \tag{23}$$

Employing Itô's differential formula, we obtain the stochastic differential as

$$dV(t)=\mathcal{L}V(t)dt+2x^T(t)P\sum_{j=1}^{q}g_j\left(t\right)d\omega_j\left(t\right), \tag{24}$$

where

$$\begin{aligned}\mathcal{L}V(t) &= 2x^T(t)Py(t)+\sum_{j=1}^{q} g_j^T(t)\,Pg_j(t)\\ &\quad +x^T(t)Qx(t)-x^T(t-\tau)Qx(t-\tau)\\ &\quad +\tau y^T(t)Sy(t)-\int_{t-\tau}^{t} y^T(\alpha)Sy(\alpha)d\alpha\\ &\quad +\sum_{j=1}^{q}\left[\tau g_j^T(t)\,Rg_j(t)-\int_{t-\tau}^{t} g_j^T(\alpha)Rg_j(\alpha)d\alpha\right].\end{aligned} \tag{25}$$

For any appropriately dimensioned matrix X, it follows from (22) that

$$2\zeta^T(t)\,X\left[x(t)-x(t-\tau)-\int_{t-\tau}^{t} y(\alpha)d\alpha-\sum_{j=1}^{q}\int_{t-\tau}^{t} g_j(\alpha)d\omega_j(\alpha)\right]=0, \tag{26}$$

where

$$\begin{aligned}\zeta^T(t) &= \left[\begin{array}{cccc} x^T(t) & x^T(t-\tau) & f^T(x(t-\tau)) & e^T\end{array}\right]^T,\\ e &= \left[\begin{array}{ccc} 1 & \cdots & 1\end{array}\right]^T\in\mathbb{R}^q.\end{aligned}$$

From Lemma 1, we obtain

$$-2\zeta^T(t)\,X\Gamma\le\zeta^T(t)\,XR^{-1}X^T\zeta(t)+\Gamma^TR\Gamma. \tag{27}$$

where

$$\Gamma=\sum_{j=1}^{q}\int_{t-\tau}^{t} g_j(\alpha)d\omega_j(\alpha).$$

By (16), for any scalar $t_j^+\ge 0$, it is clear that

$$2\sum_{j=1}^{n} t_j^+ f_j(x_j(t-\tau))\left[l_j^+x_j(t-\tau)-f_j(x_j(t-\tau))\right]\ge 0 \tag{28}$$

or, equivalently,

$$2[x^T(t-\tau)T^+L^+f(x(t-\tau))-f^T(x(t-\tau))T^+f(x(t-\tau))]\ge 0. \tag{29}$$

Similarly, for any scalar $t_j^-\ge 0$, one has

$$2\sum_{j=1}^{n} t_j^- f_j(x_j(t-\tau))\left[f_j(x_j(t-\tau))-l_j^-x_j(t-\tau)\right]\ge 0 \tag{30}$$

or, equivalently,

$$2[f^T(x(t-\tau))T^-f(x(t-\tau))-x^T(t-\tau)T^-L^-f(x(t-\tau))]\ge 0. \tag{31}$$

Then, it follows from (25)-(31) that

$$\begin{aligned}
\mathcal{L}V(t) &\leq 2x^T(t)Py(t)+\sum_{j=1}^{q} g_j^T(t)Pg_j(t) \\
&\quad +x^T(t)Qx(t)-x^T(t-\tau)Qx(t-\tau) \\
&\quad +\tau y^T(t)Sy(t)-\int_{t-\tau}^{t} y^T(\alpha)Sy(\alpha)d\alpha \\
&\quad +\sum_{j=1}^{q}\left[\tau g_j^T(t)Rg_j(t)-\int_{t-\tau}^{t} g_j^T(\alpha)Rg_j(\alpha)d\alpha\right] \\
&\quad +2\zeta^T(t)X\left[x(t)-x(t-\tau)\right]-2\zeta^T(t)X\int_{t-\tau}^{t} y(\alpha)d\alpha \\
&\quad +\zeta^T(t)XR^{-1}X^T\zeta(t)+\Gamma^TR\Gamma \\
&\quad +\tau\zeta^T(t)XS^{-1}X^T\zeta(t)-\int_{t-\tau}^{t}\zeta^T(t)XS^{-1}X^T\zeta(t)\,d\alpha \\
&\quad +2[x^T(t-\tau)T^+L^+f(x(t-\tau))-f^T(x(t-\tau))T^+f(x(t-\tau))] \\
&\quad +2[f^T(x(t-\tau))T^-f(x(t-\tau))-x^T(t-\tau)T^-L^-f(x(t-\tau))] \\
&= \digamma-\int_{t-\tau}^{t}\left[\zeta^T(t)X+y^T(\alpha)S\right]S^{-1}\left[X^T\zeta(t)+Sy(\alpha)\right]d\alpha \\
&\quad -\sum_{j=1}^{q}\int_{t-\tau}^{t} g_j^T(\alpha)Rg_j(\alpha)d\alpha+\Gamma^TR\Gamma, \qquad (32)
\end{aligned}$$

where

$$\begin{aligned}
\digamma &\triangleq 2x^T(t)Py(t)+\sum_{j=1}^{q} g^T(t)Pg(t)+x^T(t)Qx(t)-x^T(t-\tau)Qx(t-\tau) \\
&\quad +\tau y^T(t)Sy(t)+\sum_{j=1}^{q}\tau g_j^T(t)Rg_j(t)+2\zeta^T(t)X\left[x(t)-x(t-\tau)\right] \\
&\quad +\zeta^T(t)XR^{-1}X^T\zeta(t)+\tau\zeta^T(t)XS^{-1}X^T\zeta(t) \\
&\quad +2[x^T(t-\tau)T^+L^+f(x(t-\tau))-f^T(x(t-\tau))T^+f(x(t-\tau))] \\
&\quad +2[f^T(x(t-\tau))T^-f(x(t-\tau))-x^T(t-\tau)T^-L^-f(x(t-\tau))] \\
&= \zeta^T(t)\left(\Theta_1+\Theta_2+\Theta_2^T+\Xi_1+\Xi_2+\Sigma_3\right)\zeta(t), \\
\Sigma_3 &= XR^{-1}X^T+\tau XS^{-1}X^T. \qquad (33)
\end{aligned}$$

Since

$$\mathbf{E}\left\{\sum_{j=1}^{q}\int_{t-\tau}^{t} g_j^T(\alpha)Rg_j(\alpha)d\alpha\right\}=\mathbf{E}\left\{\Gamma^TR\Gamma\right\}, \qquad (34)$$

we have

$$\mathbf{E}\left\{\mathcal{L}V(t)\right\}\leq\mathbf{E}\left\{\zeta^T(t)\left(\Theta_1+\Theta_2+\Theta_2^T+\Xi_1+\Xi_2+\Sigma_3\right)\zeta(t)\right\}. \qquad (35)$$

We are now in a position to show that GRN (17) satisfies

$$\left\|z(t)\right\|_{E_2}<\gamma\sum_{j=1}^{q}\left\|n_j(t)\right\|_2 \qquad (36)$$

for all nonzero $n_j(t) \in L_2[0,\infty)$, $j = 1,\ldots,q$. Under zero initial condition, we have $\mathbf{E}\{V(0)\} = 0$ and $\mathbf{E}\{V(t)\} \geq 0$. Integrating both sides of (24) from 0 to $t > 0$ and then taking expectation, we have

$$\mathbf{E}\{V(t)\} = \mathbf{E}\left\{\int_0^t \mathcal{L}V(s)\right\} ds. \tag{37}$$

From (18), (35) and (37), it is easy to show that

$$\begin{aligned} J(t) &= \mathbf{E}\left\{\int_0^t [z^T(s)z(s) - \gamma^2 \sum_{j=1}^{q} n_j^T(s)n_j(s) + \mathcal{L}V(s)]ds\right\} - \mathbf{E}\{V(t)\} \\ &\leq \mathbf{E}\left\{\int_0^t [z^T(s)z(s) - \gamma^2 \sum_{j=1}^{q} n_j^T(s)n_j(s) + \mathcal{L}V(s)]ds\right\} \\ &\leq \mathbf{E}\left\{\int_0^t \zeta^T(s)\,[\Sigma_1 + \Sigma_2 + \Sigma_3]\zeta(s)\,ds\right\}. \end{aligned} \tag{38}$$

By Schur complement, (19) is equivalent to

$$\Sigma_1 + \Sigma_2 + \Sigma_3 < 0, \tag{39}$$

and therefore, we have

$$J(t) < 0,\ \forall t > 0. \tag{40}$$

Then, (36) follows immediately from (18) and (40) and the proof is completed. ■

Remark 2: In Theorem 1, the delays for different metabolites are assumed to be the same for simplicity only. Note that the delays may be different in real GRNs and, in this case, the GRN model (14) can be described as

$$\begin{aligned} dx(t) &= \left[Ax(t) + \sum_{i=1}^{n} B_i f(x(t-\tau_i))\right] dt + \sum_{j=1}^{q}\left[C_j x(t) + \sum_{i=1}^{n} D_{ij} f(x(t-\tau_i)) + E_j\right] d\omega_j(t), \\ z(t) &= Fx(t), \\ x(t) &= \phi(t), \quad \forall t \in [-\tau_{\max}, 0], \quad \tau_{\max} = \max\{\tau_1,\ldots,\tau_n\}. \end{aligned} \tag{41}$$

For such a generalized case, we could define the following Lyapunov-Krasovskii functional candidate for GRN (41):

$$\begin{aligned} V(t) &= V_1(t) + V_2(t) + V_3(t) + V_4(t), \\ V_1(t) &= x^T(t)Px(t), \\ V_2(t) &= \sum_{i=1}^{n}\int_{t-\tau_i}^{t} x^T(\alpha)Qx(\alpha)d\alpha, \\ V_3(t) &= \sum_{i=1}^{n}\int_{-\tau_i}^{0}\int_{t+\beta}^{t} y^T(\alpha)Sy(\alpha)d\alpha d\beta, \\ V_4(t) &= \sum_{j=1}^{q}\sum_{i=1}^{n}\int_{-\tau_i}^{0}\int_{t+\beta}^{t} g_j^T(\alpha)Rg_j(\alpha)d\alpha d\beta. \end{aligned}$$

and similar results can be obtained along the line of Theorem 1.

IV. Controller Design

This section will focus on the design of H_∞ feedback gene controller for stochastic delayed GRN (14), that is, determine the controller gain matrix K so as to guarantee that the closed-loop system (17) is mean-square asymptotically stable with the noise attenuation level γ.

Theorem 2: Given a scalar $\tau > 0$, there exists a state feedback gain matrix K such that the closed-loop system (17) is mean-square asymptotically stable with the noise attenuation level γ if there exist matrices $\hat{P} > 0$, $\hat{Q} > 0$, $\hat{S} > 0$, $\hat{R} > 0$, $\hat{T}^- = \mathrm{diag}\{\mathrm{t}_1^-, \ldots, \mathrm{t}_\mathrm{n}^-\} \geq 0$, $\hat{T}^+ = \mathrm{diag}\{\mathrm{t}_1^+, \ldots, \mathrm{t}_\mathrm{n}^+\} \geq 0$, $\hat{X}$, $\hat{K}$ satisfying

$$\hat{\Lambda} = \begin{bmatrix} \hat{\Sigma}_1 & \hat{X} & \sqrt{\tau}\hat{X} & \hat{\Phi}_1 & \hat{\Phi}_2 & \hat{\Phi}_3 \\ * & -\hat{R} & 0 & 0 & 0 & 0 \\ * & * & -\hat{S} & 0 & 0 & 0 \\ * & * & * & \hat{\Phi}_4 & 0 & 0 \\ * & * & * & * & \hat{\Phi}_5 & 0 \\ * & * & * & * & * & -I \end{bmatrix} < 0, \tag{42}$$

where

$$\begin{aligned}
\hat{\Sigma}_1 &= \hat{\Theta}_1 + \hat{\Theta}_2 + \hat{\Theta}_2^T + \hat{\Theta}_3 \\
\hat{\Theta}_1 &= W_{Q_1}^T \hat{Q} W_{Q_1} - W_{Q_2}^T \hat{Q} W_{Q_2} - 2W_f^T \hat{T}^+ W_f + 2W_f^T \hat{T}^- W_f, \\
\hat{\Theta}_2 &= W_x^T \hat{W}_y + \hat{X} W_X + W_h^T \hat{T}^+ L^+ W_f - W_h^T \hat{T}^- L^- W_f,\ \hat{\Theta}_3 = -\gamma^2 \sum_{j=1}^{q} W_{v_j}^T W_{v_j}, \\
\hat{\Phi}_1 &= \sqrt{\tau}\hat{W}_y^T,\ \hat{\Phi}_2 = \begin{bmatrix} \hat{\Upsilon}_1 & \hat{\Upsilon}_2 & \ldots & \hat{\Upsilon}_q \end{bmatrix},\ \hat{\Upsilon}_j = \hat{W}_{g_j}^T \hat{\Psi}_2,\ \hat{\Psi}_2 = \begin{bmatrix} I & \sqrt{\tau} I \end{bmatrix}, \\
\hat{\Phi}_3 &= \hat{W}_z^T,\ \hat{\Phi}_4 = -2\hat{P} + \hat{S},\ \hat{\Phi}_5 = \mathrm{diag}\left\{-\hat{\mathrm{P}}, -2\hat{\mathrm{P}} + \hat{\mathrm{R}}, \ldots, -\hat{\mathrm{P}}, -2\hat{\mathrm{P}} + \hat{\mathrm{R}}, \right\} \in \mathbb{R}^{2\mathrm{nq} \times 2\mathrm{nq}} \\
\hat{W}_y &= \begin{bmatrix} A\hat{P} + \hat{K} & 0_n & B\hat{P} & 0_n, q \end{bmatrix}, \\
\hat{W}_{g_j} &= \begin{bmatrix} C_j \hat{P} & 0_n & D_j \hat{P} & 0_{n,j-1} & E_j & 0_{n,q-j} \end{bmatrix},\ \hat{W}_z = \begin{bmatrix} F\hat{P} & 0_{n,2n+q} \end{bmatrix}.
\end{aligned} \tag{43}$$

Moreover, if the above conditions have feasible solutions, a desired controller gain matrix K is given by

$$K = \hat{K}\hat{P}^{-1}.$$

Proof: By Schur complement, (19) is equivalent to

$$\Lambda = \begin{bmatrix} \Sigma_1 & X & \sqrt{\tau}X & \Phi_1 & \Phi_2 & \Phi_3 \\ * & -R & 0 & 0 & 0 & 0 \\ * & * & -S & 0 & 0 & 0 \\ * & * & * & \Phi_4 & 0 & 0 \\ * & * & * & * & \Phi_5 & 0 \\ * & * & * & * & * & -I \end{bmatrix} < 0, \tag{44}$$

where Σ_1 is given in (20) and

$$\begin{aligned}
\Phi_1 &= \sqrt{\tau} W_y^T S,\ \Phi_2 = \begin{bmatrix} \Upsilon_1 & \Upsilon_2 & \ldots & \Upsilon_q \end{bmatrix},\ \Upsilon_j = W_{g_j}^T \Psi_2, \\
\Psi_2 &= \begin{bmatrix} P & \sqrt{\tau} R \end{bmatrix},\ \Phi_3 = W_z^T,\ \Phi_4 = -S, \\
\Phi_5 &= \mathrm{diag}\left\{-\mathrm{P}, -\mathrm{R}, \ldots, -\mathrm{P}, -\mathrm{R}, \right\} \in \mathbb{R}^{2\mathrm{nq} \times 2\mathrm{nq}}.
\end{aligned}$$

Define

$$\begin{aligned} J &= \mathrm{diag}\left\{\mathrm{J}_1, \mathrm{P}^{-1}, \mathrm{P}^{-1}, \mathrm{S}^{-1}, \mathrm{J}_2, \mathrm{I}\right\}, \\ J_1 &= \mathrm{diag}\left\{\mathrm{P}^{-1}, \mathrm{P}^{-1}, \mathrm{P}^{-1}, \mathrm{I}\right\} \in \mathbb{R}^{[3\mathrm{n}+\mathrm{q}]\times[3\mathrm{n}+\mathrm{q}]}, \\ J_2 &= \mathrm{diag}\left\{\mathrm{P}^{-1}, \mathrm{R}^{-1}, \ldots, \mathrm{P}^{-1}, \mathrm{R}^{-1}\right\} \in \mathbb{R}^{2\mathrm{nq}\times 2\mathrm{nq}}. \end{aligned} \tag{45}$$

Pre- and post-multiplying (44) with J^T and J, we obtain

$$\begin{bmatrix} J_1^T\Sigma_1 J_1 & J_1^T X P^{-1} & \sqrt{\tau} J_1^T X P^{-1} & J_1^T\Phi_1 S^{-1} & J_1^T\Phi_2 J_2 & J_1^T\Phi_3 \\ * & -P^{-1}RP^{-1} & 0 & 0 & 0 & 0 \\ * & * & -P^{-1}SP^{-1} & 0 & 0 & 0 \\ * & * & * & S^{-1}\Phi_4 S^{-1} & 0 & 0 \\ * & * & * & * & J_2^T\Phi_5 J_2 & 0 \\ * & * & * & * & * & -I \end{bmatrix} < 0, \tag{46}$$

where

$$\begin{aligned} J_1^T\Sigma_1 J_1 &= J_1^T\Theta_1 J_1 + J_1^T\Theta_2 J_1 + J_1^T\Theta_2^T J_1 + J_1^T\Theta_3 J_1 = \bar{\Theta}_1 + \bar{\Theta}_2 + \bar{\Theta}_2^T + \bar{\Theta}_3 \\ \bar{\Theta}_1 &= W_{Q_1}^T P^{-1} Q P^{-1} W_{Q_1} - W_{Q_2}^T P^{-1} Q P^{-1} W_{Q_2} - 2W_f^T P^{-1} T^+ P^{-1} W_f + 2W_f^T P^{-1} T^- P^{-1} W_f, \\ \bar{\Theta}_2 &= W_x^T P^{-1} P \bar{W}_y + J_1^T X P^{-1} W_X + W_h^T P^{-1} T^+ P^{-1} L^+ W_f - W_h^T P^{-1} T^- P^{-1} L^- W_f, \\ \bar{\Theta}_3 &= -\gamma^2 W_v^T W_v,\ \bar{W}_y = W_y J_1 = \begin{bmatrix} AP^{-1} + KP^{-1} & 0_n & BP^{-1} & 0_n, q \end{bmatrix}, \\ J_1^T\Phi_1 S^{-1} &= \sqrt{\tau} J_1^T W_y^T S S^{-1} = \sqrt{\tau}\bar{W}_y^T, \\ J_1^T\Phi_2 J_2 &= J_1^T W_g^T \Psi_2 J_2 = \bar{W}_g^T \hat{\Psi}_2,\ \bar{W}_g = W_g J_1 = \begin{bmatrix} EP^{-1} & E_d P^{-1} & E_v \end{bmatrix}, \\ \Phi_3^T J_1 &= \begin{bmatrix} FP^{-1} & 0_{n,2n+q} \end{bmatrix},\ S^{-1}\Phi_4 S^{-1} = -S^{-1}, \\ J_2^T\Phi_5 J_2 &= \mathrm{diag}\left\{-\mathrm{P}^{-1}, -\mathrm{R}^{-1}, \ldots, -\mathrm{P}^{-1}, -\mathrm{R}^{-1}\right\} \in \mathbb{R}^{2\mathrm{nq}\times 2\mathrm{nq}}. \end{aligned}$$

Letting

$$\begin{aligned} \hat{P} &= P^{-1},\ \hat{K} = KP^{-1},\ \hat{Q} = J_3 Q J_3^T, \\ \hat{X} &= J_1^T X P^{-1},\ \hat{R} = P^{-1}RP^{-1},\ \hat{S} = P^{-1}SP^{-1}, \end{aligned}$$

we obtain

$$\bar{\Lambda} = \begin{bmatrix} \hat{\Sigma}_1 & \hat{X} & \sqrt{\tau}\hat{X} & \hat{\Phi}_1 & \hat{\Phi}_2 & \hat{\Phi}_3 \\ * & -\hat{R} & 0 & 0 & 0 & 0 \\ * & * & -\hat{S} & 0 & 0 & 0 \\ * & * & * & \bar{\Phi}_4 & 0 & 0 \\ * & * & * & * & \bar{\Phi}_5 & 0 \\ * & * & * & * & * & -I \end{bmatrix} < 0, \tag{47}$$

where $\hat{\Sigma}_1$ and $\hat{\Phi}_i$ $(i = 1, 2, 3)$ are given in (43) and

$$\bar{\Phi}_4 = -S^{-1}, \bar{\Phi}_5 = \mathrm{diag}\left\{-\mathrm{P}^{-1}, -\mathrm{R}^{-1}, \ldots, -\mathrm{P}^{-1}, -\mathrm{R}^{-1}\right\} \in \mathbb{R}^{2\mathrm{nq}\times 2\mathrm{nq}}.$$

Noting $S > 0$ and $R > 0$, we have

$$\begin{aligned} S^{-1} - 2P^{-1} + P^{-1}SP^{-1} &= \left(S^{-1} - P^{-1}\right) S \left(S^{-1} - P^{-1}\right) \geq 0, \\ R^{-1} - 2P^{-1} + P^{-1}RP^{-1} &= \left(R^{-1} - P^{-1}\right) R \left(R^{-1} - P^{-1}\right) \geq 0, \end{aligned}$$

which are equivalent to

$$\begin{aligned} -S^{-1} &\leq -2P^{-1} + P^{-1}SP^{-1}, \\ -R^{-1} &\leq -2P^{-1} + P^{-1}RP^{-1}. \end{aligned} \tag{48}$$

By combining (47) and (48), we easily obtain (42). The theorem is proved. ■

Remark 3: We notice that feedback controller is of order, which means it depends linearly on the current state of the system. In real-world genetic regulatory networks, it is usually impossible to add, reduce or remove small RNA from the growth medium in practice. In terms of system description, it is also impossible to add a vector encoding the siRNA precursor such that it responds immediately and linearly to the system's state. Furthermore, due to the technological limit in synthetic biology, not all regulation mechanisms could be implemented at current stage. Therefore, there is a need to specify the structure of the controller gain K for easy realization. Given that $K = \hat{K}\hat{P}^{-1}$ in Theorem 2, if we define $\hat{P}$ as a diagonal positive definite matrix, then K will have the same structure with $\hat{K}$ which can be prespecified. This way, the structure of K can be prescribed which would help the real-time implementation.

V. Illustrative Examples

In this section, we provide an example to illustrate the results developed earlier.

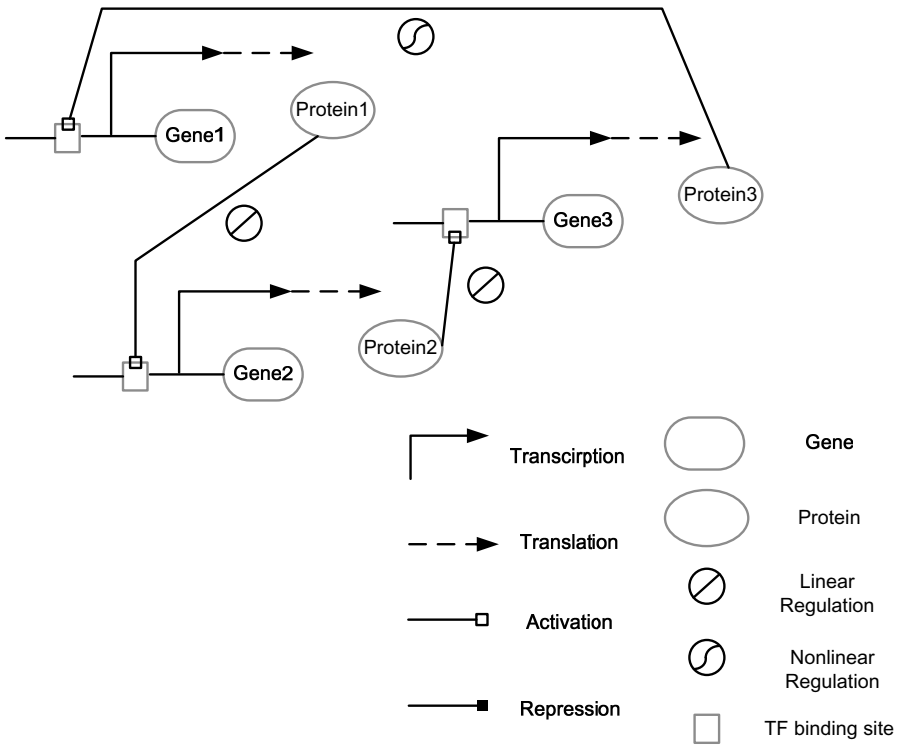

Fig. 1. A GRN described in (49) where gene product 1 activates gene 2 linearly, gene product 2 activates gene 3 linearly, gene product 3 activates gene 1 nonlinearly.

Consider the following GRN shown in Fig. 1:

$$\begin{aligned} dx(t) &= [Ax(t) + Bf(x(t-\tau))]\,dt + \sum_{j=1}^{q} [C_j x(t) + D_j f(x(t-\tau)) + E_j]\,d\omega_j(t), \\ z(t) &= Fx(t). \end{aligned} \tag{49}$$

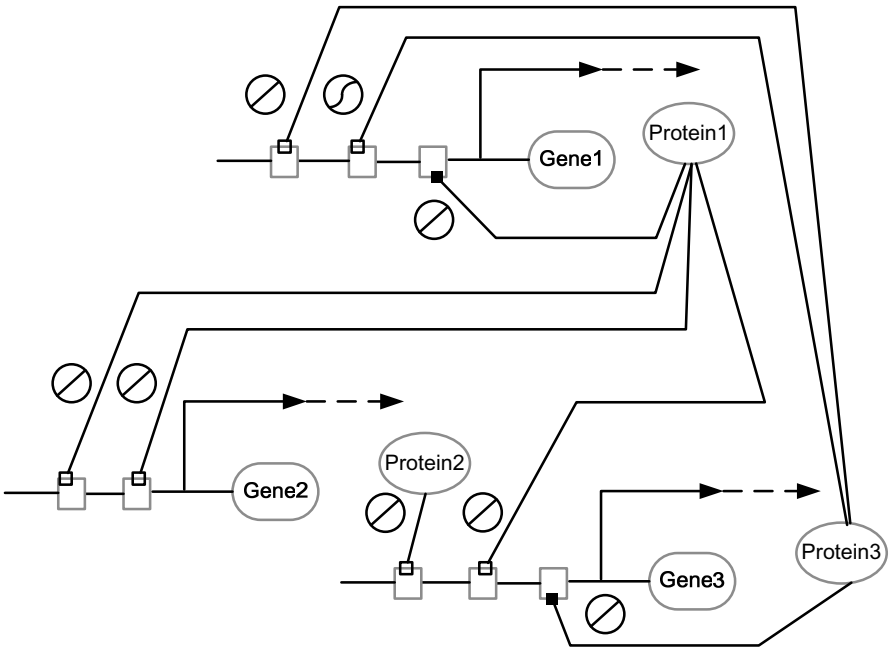

Fig. 2. Assume that gene product 2 can't regulate any genes and gene product 3 can't regulate gene 2. Two negative regulatory circuits from gene product 1 (repressor) to gene 1, gene product 3 (repressor) to gene 3 are designed. And there are three positive regulatory circuits from gene product 3 (activator) to gene 1, gene product 1 (activator) to gene 2, gene product 1 (activator) to gene 3.

where $x(t) = \left[\begin{array}{ccc} x_1(t) & x_2(t) & x_3(t) \end{array} \right]^T$ is the concentration vector of gene products (proteins) and $f(x(t-\tau)) = \left[\begin{array}{ccc} x_1(t-\tau) & x_2(t-\tau) & g(x_3(t-\tau)) \end{array} \right]^T$. The regulation from gene product 3 to gene 1 can be described by $g(x) = x^2/\left(1+x^2\right)$. It is easy to know $\dot{g}(x) \in [0, 0.65]$, and then we have $L^- = \mathrm{diag}\{1,1,0\}$ and $L^+ = \mathrm{diag}\{1,1,0.65\}$. Let the time delay $\tau = 0.03$. For simplicity, we assume the intensity of all noises to be unit and then get

$$E_1 = \left[\begin{array}{c} 1 \\ 0 \\ 0 \end{array} \right], E_2 = \left[\begin{array}{c} 0 \\ 1 \\ 0 \end{array} \right], E_3 = \left[\begin{array}{c} 0 \\ 0 \\ 1 \end{array} \right], E_4 = \left[\begin{array}{c} 1 \\ 1 \\ 1 \end{array} \right],$$

which indicates that there are four noise sources, where the noises ξ_1, ξ_2 and ξ_3 can only affect specific pathway respectively while ξ_3 can affect the global pathway.

The system matrices are given as follows:

$$\begin{aligned}
A &= \text{diag}\{-0.0985, -5, -3\}, \mathrm{B} = \begin{bmatrix} 0 & 0 & -0.3962 \\ 0.1971 & 0 & 0 \\ 0 & 2 & 0 \end{bmatrix}, \\
C_1 &= \text{diag}\{-0.0828, 0, 0\}, \mathrm{C}_2 = \text{diag}\{0, -2.8000, 0\}, \\
C_3 &= \text{diag}\{0, 0, -2.1000\}, \mathrm{C}_4 = \text{diag}\{-0.0355, -1.2000, -0.9000\}, \\
D_1 &= \begin{bmatrix} 0 & 0 & -0.3328 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \; D_2 = \begin{bmatrix} 0 & 0 & 0 \\ 0.1379 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \\
D_3 &= \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1.4000 & 0 \end{bmatrix}, \; D_4 = \begin{bmatrix} 0 & 0 & -0.1426 \\ 0.0591 & 0 & 0 \\ 0 & 0.6000 & 0 \end{bmatrix}.
\end{aligned}$$

We let $F = [0, 0, 1]$, which means that we are only interested in gene product 3.

For a given $\gamma = 10$, we can obtain a feasible solution by solving the condition in Theorem 2 using the LMI toolbox in Matlab and obtain

$$\hat{P} = \text{diag}\{127.5927, 1.5568, 45.9005\},$$

According to the control scheme described in Fig. 2, we calculate feedback controller gain K as

$$K = \begin{bmatrix} -61.1547 & 0 & 0.2287 \\ 0.1499 & 0 & 0 \\ 0.1724 & 0 & -56.7174 \end{bmatrix}.$$

The simulation results of the trajectories of $x_3(t)$ without and with control are shown in Fig. 3 and Fig. 4 with zero initial conditions respectively, which clearly show that our developed design scheme is indeed useful.

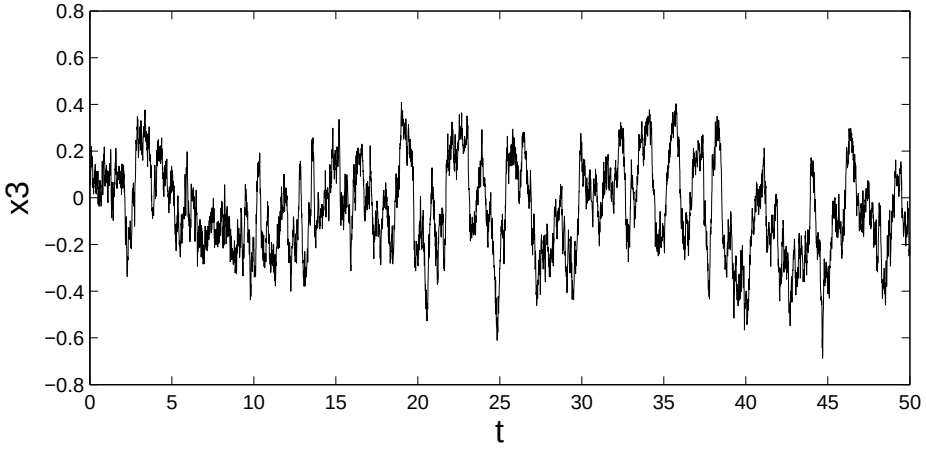

Fig. 3. Trajectories of gene 3 product in GRN (49) without control

VI. Conclusions

In this paper, we have investigated the problem of gene feedback control for stochastic delayed GRNs. A delayed stochastic model with additive and multiplicative noise is utilized to describe the GRNs. We have

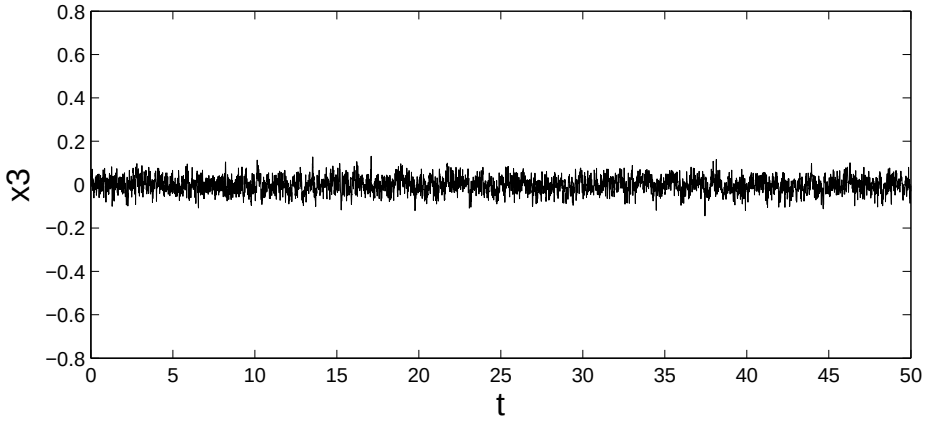

Fig. 4. Trajectories of gene 3 product in GRN (49) with control

considered both the intrinsic and extrinsic noises which are introduced to model kinetic parameter variations and basal rate disturbance. Then, we have focused on the H_∞ feedback controller design and specify the structure of controller gain according to engineering practice. The merit of the obtained results lies in that a Lyapunov-Krasovskii functional has been utilized using the stochastic analysis approach. An example has demonstrated that the designed GRN can achieve perfect noise attenuation under control, which will facilitate the experiment and reduce the cost in both synthetic biology and systems biology.

References

[1] P. Swain, M. Elowitz, and E. Siggia, Intrinsic and extrinsic contributions to stochasticity in gene expression, Proceedings of the National Academy of Sciences, vol. 99, no. 20, pp. 12795–12800, 2002.

[2] M. Thattai and A. van Oudenaarden, Intrinsic noise in gene regulatory networks, Proceedings of the National Academy of Sciences, pp. 8614–8619, 2001.

[3] E. Ozbudak, M. Thattai, I. Kurtser, A. Grossman, and A. van Oudenaarden, Regulation of noise in the expression of a single gene, Nature Genetics, vol. 31, no. 1, pp. 69–73, 2002.

[4] M. Elowitz, A. Levine, E. Siggia, and P. Swain, Stochastic Gene Expression in a Single Cell, pp. 1183–1186, 2002.

[5] J. Paulsson, Summing up the noise in gene networks, Nature, vol. 427, pp. 415–418, 2004.

[6] J. Pedraza and A. van Oudenaarden, Noise Propagation in Gene Networks, Science, vol. 307, no. 5717, pp. 1965–1969, 2005.

[7] J. Raser and E. O'Shea, Noise in Gene Expression: Origins, Consequences, and Control, Science, vol. 309, no. 5743, pp. 2010–2013, 2005.

[8] H. McAdams and A. Arkin, Stochastic mechanisms in gene expression, Proceedings of the National Academy of Sciences, vol. 94, no. 3, p. 814, 1997.

[9] J. Hasty, D. McMillen, and J. Collins, Engineered gene circuits, Nature, vol. 420, no. 6912, pp. 224–230, 2002.

[10] C. Rao and A. Arkin, Stochastic chemical kinetics and the quasi-steady-state assumption: Application to the Gillespie algorithm, The Journal of Chemical Physics, vol. 118, p. 4999, 2003.

[11] B. Munsky and M. Khammash, Transient analysis of stochastic switches and trajectories with applications to gene regulatory networks, IET Systems Biology, vol. 2, no. 5, pp. 323–333, 2008.

[12] M. Khammash, Stochastic analysis of noisy gene expression, Proc. 3rd IEEE International Symposium on Control, Communications and Signal Processing (ISCCSP 2008), pp. 141, 2008, St Julians, Malta.

[13] H. Risken, The Fokker-Planck Equation, Applied Optics, vol. 28, no. 20, pp. 4496–4497, 1989.

[14] N. Kampen, Stochastic processes in physics and chemistry. North-Holland New York, 1992.

[15] D. Gillespie, Exact stochastic simulation of coupled chemical reactions, The Journal of Physical Chemistry, vol. 81, pp. 2340–2361, 1977.

[16] U. Alon, An Introduction to Systems Biology: Design Principles of Biological Circuits. Chapman & Hall/CRC, 2007.

[17] E. Voit, Computational Analysis of Biochemical Systems: A Practical Guide for Biochemists and Molecular Biologists. Cambridge University Press, 2000.

[18] M. Elowitz and S. Leibler, A synthetic oscillatory network of transcriptional regulators. Nature, vol. 403, no. 6767, pp. 335-8, 2000.

[19] Y. Yokobayashi, R. Weiss, and F. Arnold, Directed Evolution of a Genetic Circuit, Proceedings of the National Academy of Sciences of the United States of America, vol. 99, no. 26, pp. 16587–16591, 2002.

[20] N. Wiener, Cybernetics Or Control and Communication in the Animal and the Machine. MIT Press, 1961.

[21] C. Tomlin, Understanding biology by reverse engineering the control, Proceedings of the National Academy of Sciences, vol. 102, no. 12, pp. 4219–4220, 2005.

[22] Z. Wang, H. Qiao, and K. Burnham, On stabilization of bilinear uncertain time-delay stochastic systems with Markovian jumping parameters, IEEE Transactions on Automatic Control, vol. 47, no. 4, pp. 640–646, 2002.

[23] F. Yang, Z. Wang, Y. Hung, and M. Gani, H_∞ control for networked systems with random communication delays, IEEE Transactions on Automatic Control, vol. 51, no. 3, pp. 511–518, 2006.

[24] J. Doyle, K. Glover, P. Khargonekar, and B. Francis, State-space solutions to standard H_2 and H_∞ control problems, IEEE Transactions on Automatic Control, vol. 34, no. 8, pp. 831–847, 1989.

[25] J. Hasty, J. Pradines, M. Dolnik, and J. Collins, Noise-based switches and amplifiers for gene expression, Proceedings of the National Academy of Sciences, vol. 97, no. 5, pp. 2075–2080, 2000.

[26] C. Rao, D. Wolf, and A. Arkin, Control, exploitation and tolerance of intracellular noise, Nature, vol. 420, no. 6912, pp. 231–237, 2002.

[27] C. Li, L. Chen, and K. Aihara, Stability of Genetic Networks With SUM Regulatory Logic: Lur'e System and LMI Approach, IEEE Transactions on Circuits and Systems I: Regular Papers, vol. 53, no. 11, pp. 2451–2458, 2006.

[28] C. Li, L. Chen, and K. Aihara, Stochastic stability of genetic networks with disturbance attenuation, IEEE Transactions on Circuits and Systems II: Express Briefs, vol. 54, no. 10, pp. 892–896, 2007.

[29] C. Li, L. Chen, and K. Aihara, Stochastic synchronization of genetic oscillator networks, BMC Systems Biology, vol. 1, Art. no. 6, 2007.

[30] F. Ren and J. Cao, Asymptotic and robust stability of genetic regulatory networks with time-varying delays, Neurocomputing, vol. 71, no. 4-6, pp. 834–842, 2008.

[31] H. de Jong, Modeling and Simulation of Genetic Regulatory Systems: A Literature Review, Journal of Computational Biology, vol. 9, no. 1, pp. 67–103, 2002.

[32] B. Chen and W. Wu, Robust filtering circuit design for stochastic gene networks under intrinsic and extrinsic molecular noises, Mathematical Biosciences, vol. 211, no. 2, pp. 342–355, 2008.

[33] B. Chen and P. Chen, Robust Engineered Circuit Design Principles for Stochastic Biochemical Networks With Parameter Uncertainties and Disturbances, IEEE Transactions on Biomedical Circuits and Systems, vol. 2, no. 2, pp. 114–132, 2008.

[34] B. Chen, Y. Chang and Y. Wang, Robust H_∞-stabilization design in gene networks under stochastic molecular noises: fuzzy-interpolation approach, IEEE Transactions on System, Man and Cybernetics Part B: Cybernetics , Vol. 38, No. 1, pp. 25–42, 2008.

[35] Z. Wang, J. Lam, G. Wei, K. Fraser and X. Liu, Filtering for nonlinear genetic regulatory networks with stochastic disturbances, IEEE Transactions on Automatic Control, Vol. 53, No. 10, pp. 2448–2457, Nov. 2008.

[36] Z. Wang, F. Yang, D. W. C. Ho, S. Swift, A. Tucker and X. Liu, Stochastic dynamic modeling of short gene expression time series data, IEEE Transactions on NanoBioscience, Vol. 7, No. 1, pp. 44-55, Mar. 2008.

[37] Y. Wang, L. Xie, and C. de Souza, Robust control of a class of uncertain nonlinear systems, Systems & Control Letters, vol. 19, no. 2, pp. 139–149, 1992.

[38] S. Boyd, L. El Ghaoui, E. Feron, and V. Balakrishnan, Linear Matrix Inequalities in System and Control Theory. Society for Industrial Mathematics, 1994.